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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
09/185,408	11/03/98	SZKUDLINSKI	M EXAMINER

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ART UNIT	PAPER NUMBER
1647	7

DATE MAILED: 08/02/00

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 5/18/00

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-80 is/are pending in the application.

Of the above, claim(s) 18-23, 26, 54-64, 73, 79, 80 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-17, 24, 25, 27-53, 65-72, 74-78 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims 1-80 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

Part III: Detailed Office Action

Notice: Effective June 18, 2000, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit **1647**.

Restriction Requirement:

Applicant's election without traverse of Invention I, and species thyroid stimulating hormone in Paper No. 6 filed 5/24/00 is acknowledged.

Claims 18-23, 26-29, 54-67, 73, 79 and 80 are withdrawn from further consideration pursuant to 37 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention or species, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 6.

The restriction requirement is withdrawn with respect to group II, claims 27-29 and 65-67, on the basis that the claimed proteins may only be made, in a practical sense, via recombinant DNA technology.

Claims 1-17, 24, 25, 27-53, 65-72 and 74-78 are under consideration.

Formal Matters and Objections:

Claim 47 is objected to under 37 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form. Claim 47 recites limitations identical to the claim from which it depends, and thus is not further limiting.

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78). Correction is required.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17, 24, 25, 27-53, 65-72 and 74-78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "human" glycoprotein hormone, as used in all of the claims, is indefinite. It is noted that the specification defines the term at page 7. However, the definition proffered therein is both relative and subjective, as it defines "human" only in terms of what other sequence the claimed sequence is being compared to. As there is no basis for comparison in the claims, e.g. the claims do not state that the protein is "human" as determined relative to bovine, for example, the claims are indefinite. The definition of 'nonchimeric' as found at page 8 of the specification and as recited in claim 75, for example, is similarly indefinite.

Claims 13 and 50 are indefinite for reciting "the b-subunit". Amendment to read "the beta subunit" would be remedial.

Claims 15-17 are indefinite for failing to specify that the indicated residues (58, 63 or 69) are in the beta subunit. Claims 51-53 are similarly indefinite.

Claims 24 and 25 are indefinite for reciting "the basic amino acids"; the antecedent basis for such is not clear. The claims should be amended to recite "*said* basic amino acids".

Claims 32-35 and 69-72 are indefinite for reciting "the a-subunit", and should be amended to recite "the alpha subunit", to be remedial.

Claim 34 is indefinite as the meaning of "the hormone human glycoprotein hormone" is unclear. Further, it is unclear how the human glycoprotein hormone could *not* have complete homology with itself. It is suggested that the claim be amended to indicate that "*said* human glycoprotein hormone has complete amino acid sequence homology with the *corresponding wild-type* human glycoprotein hormone...".

Claim 37 is duplicative of claim 36.

There is no antecedent basis for "the basic amino acid residue" as recited in claims 42, and 44-46. In the case of claims 44-46, it is not clear whether the recited positions are the only basic amino acid residues, or whether there may be others.

Claim 68 is indefinite due to grammatical mistakes, especially the use of the word 'having'; it would appear that 'has' would be clearer. Also, it is not clear how a protein can be further modified to have *less* than a given number of substitutions.

Claim 74 is indefinite because it states that the hormone comprises a basic amino acid substituted at a position corresponding to the homologous amino acid position in a more active non-human glycoprotein hormone homolog; it would appear that *all* positions correspond to a homologous amino acid position of a non-human homolog, and further, it is not clear what the non-human homolog is to be more active *than,* i.e. to what it is being compared, or under what conditions. Additionally, it is not clear how a hormone 'having increased activity' is produced by substitution from a 'more active' homology; each cannot be more active than the other. Claim 75 is similarly indefinite. Also, in addition to being indefinite for recitation of 'nonchimeric', as discussed above, claim 75 is indefinite for reciting 'correspondig' at line 2; amendment to read 'corresponding' would be remedial.

Any remaining claims are rejected for depending from an indefinite claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 74-78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while providing and adequate written description and enablement of human TSH muteins having lysine substitutions at α subunit positions 11, 13, 14, 16, 17 and 20 which have increased TSH

activity, or having an arginine substitution at position 69 of the β subunit and increased TSH activity, does not reasonably provide written description or enablement for any other substitutions, either in TSH or in others of the glycoprotein hormones, which result in increased hormone activity.

The specification, specifically at Table II, demonstrates a reasonable number of the above-mentioned species to have increased hormone activity, and it is reasonably predictable that other combinations of those substitutions would be similarly increased. However, the same table shows that the effects of other substitutions, e.g. β R67K do not have similar effects, and it is not predictable which other possible substitutions would have the intended effect. Glycoprotein hormone sequences are known from a wide variety of organisms, from humans to fishes. There is a very large number of substitutions that could be made in the human hormones. Although applicants have demonstrated a limited number of substitutions to increase hormone activity in TSH, it is not predictable that those results can be directly extrapolated to the other glycoprotein hormones, nor that even a commensurate number of TSH substitutions are enabled. The effects of such substitutions cannot be predicted in advance. The disclosure of seven substitutions is not commensurate in scope with claims to any substitution which may serve to increase the biological activity of TSH, much less others of the glycoprotein hormones. Although the skill in the art is high, what would be required would be to synthesize each individual species and assay for activity. Although the specification has disclosed seven species within the metes and bounds of the claims, the specification does not provide adequate basis for predicting, *a priori*, additional functional species. The general concept of hormones with increased activity is merely a wish. The actual inventive step in this case appears to be the actual determination of which species have those properties, and the specification has not taught how to predict such. Although it is suggested to substitute residues from homologous proteins, even this is not a predictable process, and there is no *a priori* method of predicting which of such substitutions will have which results.

This case is similar to that decided in *Amgen v.* Chugai, 18 USPQ 2d 1017(1991), wherein it was found that conception may not be achieved until reduction to practice in cases involving cloning genes. In this case, conception is the realization of species having increased activity, and that

conception is not realized until the species has been made and tested.

A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of *Genentec, Inc, v. Novo Nordisk*, 42 USPQ 2d 100,(CAFC 1997), the court held that:

> "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

The instant specification is not enabling because one cannot, following the guidance presented therein, practice the claimed method without first making a substantial inventive contribution, in this case, synthesizing and testing each individual species. That process of making and testing constitutes the actual conception of the invention. The only species for which there is adequate written description are those which have been made and shown to be functional. Thus, the specification does not provide an adequate written description or enablement of a commensurate number of the claimed species.

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 11, 24, 25, 27-32, 35-37, 40-47, 65-70, and 74-78 are rejected under 35 U.S.C. 102(b) as being anticipated by Campbell et al., WO91/16922.

Campbell et al. teach numerous analogues of glycoprotein hormones. The analogues were made by recombinant DNA methodology, involving construction of appropriate nucleic acids, vectors and host cells. At page 1 they teach that the hormones are either homodimeric or heterodimeric, and that in heterodimers, "the chemical structure of the beta-subunit or the alpha-subunit or both may be different from that of the native hormones." See page 1, lines 20-23. Specifically, analogues H1-H3, H6, H8 and H10 have lysine residues at positions 11, 13, 16 and 20 of the human α subunit. Analog H2 has only 2 substitutions in addition to those at the recited positions. Analogues H1-H8 are shown to have activity in dimerizing with hCGβ, and to bind to LH receptor, see table XIV at page 73. At table III, page 62, analogues C1-C9 are disclosed. These are chimeras between hCG and hTSHβ. Chimeras C1-C9 all comprise TSHβ amino acid sequences, and each meet the limitation of having a basic residue at at least one of positions 58, 63 or 69 of the β subunit, and therefore meet the limitations of the claims. Although Campbell et al. did not appreciate an increase in hormone activity, such would have been inherent to the disclosed α subunit muteins, as evidenced by the data in applicant's specification. Note that the Examiner is not using applicants disclosure against applicant, rather the disclosure merely provides evidence of the inherency of the claimed property.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12-17 and 48-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell et al. The teachings of Campbell et al. are cited above in the rejection under 35 U.S.C. §102(b). Although Campbell et al. teach α subunits within the scope of the claims, and additionally teach β subunits within the scope of the claims, Campbell et al. do not specifically teach the combination of the particular α with the particular β subunits. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the modified α and β subunits to form a heterodimeric hormone in view of the fact that the glycoprotein hormones are heterodimeric in nature. One of ordinary skill in the art would have been motivated to do so by Campbell's teaching at page 1 that the altered subunits may be so combined, and by the fact that the single α subunit combines with each of the four β subunits in forming functional hormones; thus, it would have been obvious to substitute the mutated hTSHβ subunits disclosed by Campbell et al. into the heterodimers comprising the mutated α subunits as taught by Campbell et al. In view of the fact that the α subunits were shown to be functional (Table XIV), and that Campbell et al. expected the β subunits to be useful as TSH antagonists (page 23), one would have expected to be successful at forming a heterodimeric hormone comprising the mutated α and β subunits.

Advisory Information:

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 8:00 A.M. to 4:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (703)308-4623.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 305-4242. Faxed draft or informal communications with the

examiner should be directed to (703) 308-0294. **Please** advise the Examiner at the telephone number above when an informal fax is being transmitted.

Lorraine Spector, Ph.D.
Primary Examiner

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